Don’t Sweat It: A Wearable Stress Monitor

Author: Cristina McLaughlin

Date: December 2, 2020
Class: EE681

Abstract: Cortisol, glucose, lactate, and other enzymes are important indicators of physiological health. Recent research has shown that there is a strong correlation between analytes found in sweat and concentrations found in blood. Don’t Sweat It is a watch device that relies on amperometric biosensing to collect and analyze analyte concentrations in sweat continuously and in real-time. The feedback will be beneficial in both clinical and non-clinical settings to aide in diagnoses, daily monitoring, and lifestyle changes. Don’t Sweat It will be classified as Class II De Novo device and can gain approval in 150 days or less.

1 Introduction

1.1 Motivation

In 2020, the COVID-19 pandemic has spotlighted numerous issues within our society and brought medical, financial, social, and emotional hardships to many individuals across the globe. According to the American Psychological Association the average reported stress related to the pandemic for adults in the United States is 5.9 [1]. This is significantly higher than the value reported last year which was 4.9. The Kaiser Family Foundation also revealed that more than one in three adults have reported symptoms of anxiety or depressive order starting in May 2020, while in comparison, about one in ten adults reported the same symptoms in 2019 [2]. The pandemic has greatly contributed to the growing national epidemic of chronic stress.

Cortisol is known as the “stress hormone”. It is a steroid hormone that is produced and controlled by the hypothalamus, the pituitary gland, and the adrenal gland. Almost every cell has a cortisol receptor meaning that the hormone can have a huge impact on many different bodily functions [3]. Unfortunately, too much cortisol over prolonged periods of time can lead to health problems like anxiety, depression, digestive and sleep problems, weight gain, and even diminished memory or concentration. In women, high cortisol can even contribute to changes in libido and menstrual cycles [4].

While there are multiple ways to keep cortisol levels under control by relaxing the body, there are many challenges that prohibit some people from maintaining healthy stress levels. For instance, individuals respond differently to cortisol secretion; some people feel overwhelmed with low levels, and these reactions can change throughout a person’s life. People experiencing depression also have elevated cortisol levels [3]. Others may not be able to recognize the physical signs of chronic stress meaning they believe their symptoms are a normal part of their lifestyle.

1.2 What is Don’t Sweat It?

Don’t Sweat It is a wearable sensor used to primarily monitor cortisol levels. It is intended for over-the-counter use. It is designed to continuously collect, analyze, record, and display a user’s cortisol levels obtained from sweat samples. Don't Sweat It can also sense for other metabolites in sweat like glucose and lactate to give the user a bigger picture of their overall health. The enzyme testing only requires a low volume of sweat so a user does not have to be active for the device to provide an accurate reading [5]. The watch then acquires and analyzes the concentration of cortisol or other metabolites indicated from the enzymatic amperometric sensor. Finally, it saves or displays the data in real-time. The watch screen shows the cortisol, glucose, and lactate levels through the day and average levels calculated.

1.3 Applications: Clinical and Non-Clinical

This device has many use cases from diagnoses to everyday monitoring. For instance, typical cortisol blood tests require the patient to have blood drawn in the morning and evening. The experience itself can induce stress and skew the patient's test results. Unlike blood tests, Don't Sweat It can collect data as the patient goes through daily life, at all times of the day. This can provide useful information for identifying chronic stress, Cushing disease or syndrome, depression, and anxiety [3]. Similarly, since the device will also monitor lactate and glucose levels, it can be used to diagnose diseases related to higher levels of these metabolites. For instance, when lactate levels climb too high it indicates sepsis and septic shock, however it can also signal other important conditions too [6]. If Don't Sweat It records consistently high levels of glucose, it could also aide physicians in identifying prediabetic individuals.

In non-clinical settings the device can also help individuals monitor their own cortisol, glucose, and lactate levels continuously. Like the fitness trackers discussed above, Don't Sweat It would be for consumers who want an aide and motivation for lifestyle changes. The cortisol monitor would allow users to recognize when their stress levels are heightened by providing real data feedback. It would also help them recognize types of destressing techniques that actually work. Next, glucose monitoring would be beneficial for those who are diabetic or conscious about their sugar intakes. Finally, users likely would not monitor their own lactate levels because it is more for clinical usage.

1.4 Potential Users

The estimated number of potential users would be similar to users of other popular wearable devices, glucose monitors, and meditation apps. These devices share the same targeted audience as Don't Sweat It.

Fitbit has about 30 million active users [7]. According to the CDC, about 1 in 10 Americans, over 34.2 million, have diabetes, indicating they also likely use glucose monitors [8]. Lastly, the app market for meditation, stress, and anxiety has also exploded. Calm, one of the most popular meditation apps, had 60 million downloads in 2020 and 2 million paid subscribers in 2019 [9]. Since it's more niche than Fitbit we predict it would not gain as large of an audience, so we used 30 million as a ceiling estimate. However, it would still pull in users of glucose monitors and stress apps. We would estimate about 15-20 million active users at its peak usage.

The organization of this report follows. Section 2 contains background information on wearable sensors, sweat as a biofluid, and the sweat indicators that Don't Sweat It will target. Section 3 explains the design of the proposed device as well as a breakdown of the cost and materials. Next, Section 4 details the device's path to FDA approval. Lastly, Section 5 concludes the report.

2 Background

2.1 State of the Art Wearable Sensors

The idea of wearable sensors to monitor daily health is not a new concept. Consumer products such as the Apple Watch, Fitbit, and Garmin Vivosmart are fitness trackers that motivate individuals to make healthier choices. These products focus on collecting data through physical means like heart rate sensed as a pulse point, temperature, and accelerometry. On the other hand, there are products like FreeStyle Libre which is a continuous glucose monitoring system; it operates using a thin flexible filament that is inserted under the skin and kept in place throughout the day [10]. Products like these collect and analyze biochemical data through blood. Don't Sweat It is an evolution of these devices that will collect noninvasively through sweat instead.

2.2 Perspiration as a Biofluid

Perspiration is a form of thermoregulation within the body. An average adult can secrete between 500 to 700 ml of fluid from the sweat glands daily [11]. Sweat is an easily accessible biofluid that is rich with physiological data. However, all analytes exhibit different correlations between sweat and blood concentrations [12]. For instance, steroid hormones like cortisol and testosterone have a strong blood-sweat correlation. This is due to how the biomarker enters the sweat through a more direct route. Larger analytes like glucose, lactate, and urea have had ongoing debate regarding the exact correlation between sweat and blood concentrations. However, there has been recent research indicating a stronger correlation between glucose and blood than previously shown [13]. Sweat based sensors have also already been developed and tested in detecting glucose, ethanol, pH, calcium, and lactate [14]. Sweat is a useful and accessible biofluid that can provide a way for continuous monitoring health.

2.3 Targeted Perspiration Analytes

Don't Sweat It will analyze sweat for several key analytes: cortisol, lactate, and glucose. As stated in the introduction, the focus of Don't Sweat It is as a stress monitor and cortisol is the stress hormone. Lactate in sweat has been studied and shown to correlate to physiological performance and panic disorder [6]. Glucose levels are important in indicating hyperglycemia and hypoglycemia, which may cause symptoms like nausea and blurred vision or shakiness and anxiety, respectively [15]. Expanding Don't Sweat It to include analytes in addition to cortisol and stress indicators, makes the device more robust and useful in overall health monitoring.

2.4 Enzymatic Amperometric Sensors

Amperometric sensors collect data by measuring current generated by enzymatic or biochemical reactions at the surface of the electrode [16]. The reaction creates a potential difference between the working electrode and reference electrode shown in Figure 1. Amperometric sensors have proven to be useful in biosensing tools because of ease of fabrication and disposability. These types of sensors also provide robust data on the targeted analyte because the potential reaction can be tailored to only match the molecule being tested for [16]. For instance, when testing for metabolites like glucose or uric acid, the enzyme recognition element is tethered to the working electrode. The targeted enzyme then creates a potential through a *reduction-oxidation* (redox) reaction with the enzyme recognition element that was tethered.

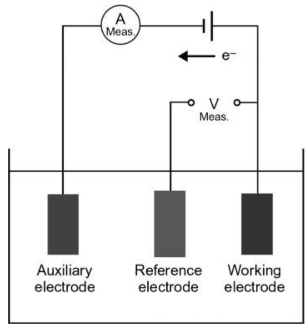

Figure 1. Amperometric sensor schematic [16]

Don't Sweat It will rely on enzymatic amperometric sensors to test for the analytes described in Section 2.3. All the analytes are metabolites and can be sensed using this method. Cortisol, glucose, and lactate would be sensed by inducing a redox with cortisol oxidase, glucose oxidase, and lactate oxidase, respectively.

4 Design and Fabrication

4.1 Block Diagram

The design of Don't Sweat It combines a variety of components from wearable devices and sweat sensors. The main component is the enzymatic amperometric biosensor that is used to measure the concentration of the targeted analytes in sweat. Figure 2 on page 8 shows a zoomed in block diagram of how the biosensor works. The analyte oxidase that is tethered to the electrode array creates a redox reaction with either cortisol, glucose, or lactate, then the electron transfer creates a measurable current. The oxidase is not consumed in the redox reaction so the reaction can continuously occur until the enzyme oxidase denatures. Enzymes can remain active at room temperature for one to three weeks [17]. The biosensor will be packaged as a cartridge that is inserted into the watch base; the cartridge is disposable, replaceable, and will last for up to 2 weeks of use.

Figure 3 on page 8 shows the full Don't Sweat It sensor along with its inputs and outputs. Sweat is absorbed by a wick and wets the surface of the amperometric biosensors. Each enzyme sensor shown in the yellow highlighted block contains an individual amperometric sensor that is detailed in Figure 2. The sensors generate current signals proportional to the abundance of the targeted sweat analyte. The current is then fed into a transimpedance amplifier that converts the current into a voltage signal. An inverter and low-pass filter are used to tune the signal range to stay within the input voltage range of the analog to digital signal converter. Next, the signal is converted and sent to a microcontroller that can analyze the signals, record data, and conduct data manipulation to obtain the mean and median values of the analytes over a period of time. Finally, there are two modes of output for user interaction: an LED display on the watch face and a phone app that can connect through Bluetooth.

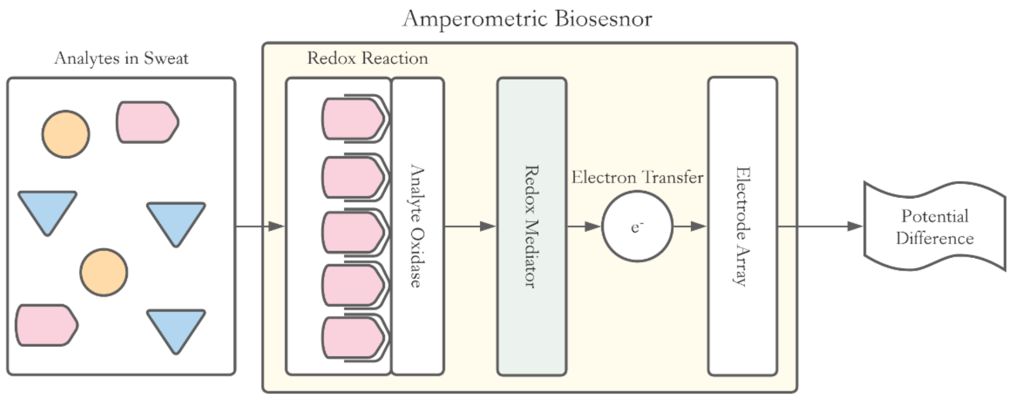

Figure 2. Detailed view of enzymatic amperometric biosensor.

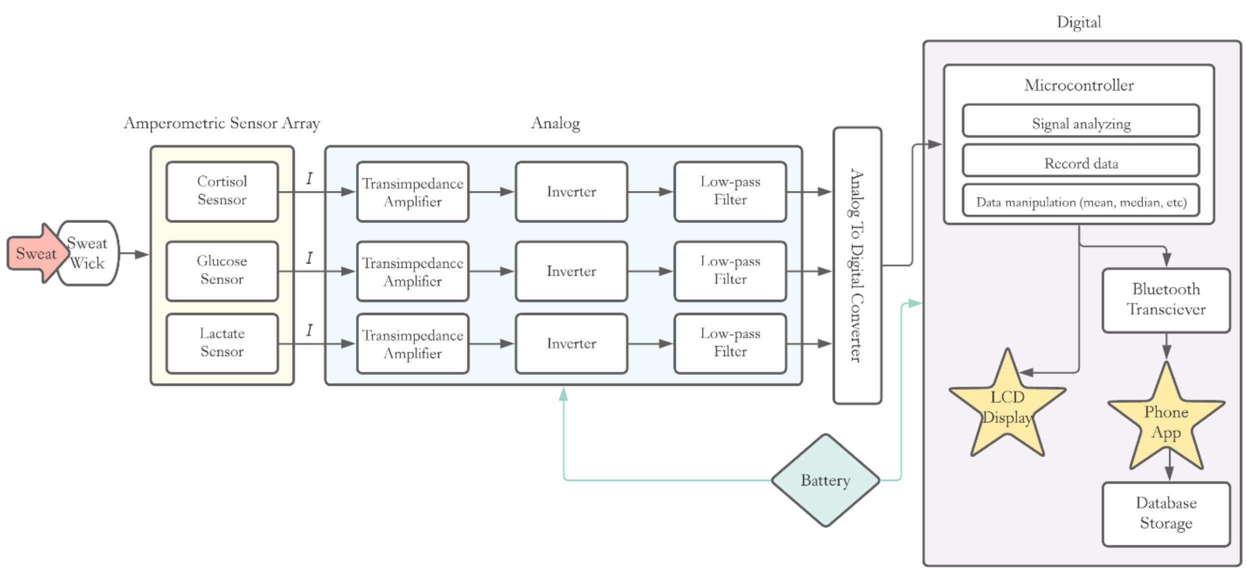

Figure 3. Block diagram of device hardware

4.2 Product Design and Cost

The estimated size of Don't Sweat It will be around the size of a typical wristwatch and maintain a low profile of about 10.4mm. The watch face will contain an LCD screen that is 128px by 128px and 1.44" diagonally. The back of the watch will be enclosed, besides a small port for the disposable sensor array to connect to. Figure 4 shows a diagram of the watch design and disposable sensor array. The plastic sensor array will then be pressed against the user's wrist to collect sweat while the watch is worn. The watch housing will contain the rest of the circuitry outlined in the block diagram. The side of the watch will also have a port to recharge the lithium battery.

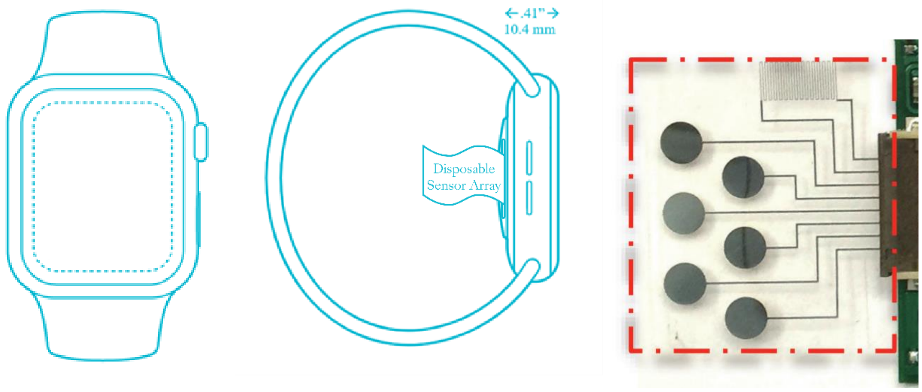

Figure 4. Watch size, design, and sensor array (left to right)

The following section estimates the hardware costs. The parts list, part number, and cost per unit is shown in Table 1. Costs were gathered from BuyDisplay for the LCD screen and Mouser for all other device parts. The EFM32 Tiny Gecko 32-bit Microcontroller was recommended for wearable devices because of its high performance, but ultra-low power consumption in active, sleep, and deep sleep modes. It also features extra peripherals like 3 operational amplifiers, an analog to digital converter, and an LCD controller meaning these components do not need to be bought separately or factored into the cost.

The disposable amperometric sensor array was more difficult to estimate the cost for. According to Weltin and Kieninger, amperometric sensor systems are "easily miniaturized and fabricated with microfabrication technologies" [18]. It is possible to screen-print the electrodes on a flexible substrate wafer, then bind the necessary enzyme oxidases to each electrode [18]. The wafer can then be cut into multiple disposable strips. Most references described this process as very low cost, but did not provide specific cost estimates, so the sensor will be excluded from the total price. Therefore, the total cost of the electronic hardware required for Don't Sweat It totals $41.01.

Table 1. Hardware parts and cost

Hardware	Model Number	Cost Per Unit	Units	Total Cost
1.44" TFT LCD Display	ER-TFTM1.44-2	\$3.84	1	\$3.84
3.7V 1200mAh Lithium Ion Battery	Adafruit 258	\$9.95	1	\$9.95
Transimpedance Amplifier	OPA857IRGTT	\$6.24	3	\$18.72
6 Gate Inverter	SN74HCS14	\$0.38	1	\$0.38
Bluetooth Module	BGX13S22GA-V21R	\$5.88	1	\$5.88
EFM32 Tiny Gecko 32-bit Microcontroller	EFM32TG210F32-D-QFN32	\$2.24	1	\$2.24
		Total Cost		**\$41.01**

4.3 Power Consumption

This section discusses the total power consumption and the battery life of the device. The sensor array does not require a power source to work because the redox reaction autonomously generates current. Therefore, the battery only needs to power the LCD display, the 3 transimpedance amplifiers, the inverter, Bluetooth transceiver, and microcontroller. The total power consumption of all the components can be calculated using the equations shown below:

$$P = V \times I \qquad \text{(Eqn. 1)}$$

The following values have been collected from each component's datasheet. The microcontroller will switch between deep sleep (1.0μA @ 3V), sleep (51μA @ 3V), and run mode (150μA @ 3V) [19]. Both sleep modes can still autonomously monitor the amperometric sensors, so the watch still collects data throughout the day while also saving energy. Run mode would be used when the user wants to display data to the screen or access it over Bluetooth connection. Using the equation above, deep sleep, sleep, and run mode each dissipate 3μW, 153μW, 450μW, respectively. Therefore, the average power dissipation by the microcontroller is 202μW. The LCD screens operates using 25mA @ 3V or 75mW [20]. It will remain off when the microcontroller is in sleep or deep sleep mode, so the power dissipation will be halved to 37.5mW. The three transimpedance amplifiers require 23. mA @ 3—all three will dissipate a total of 210.6mW [21]. The inverter has very low power consumption 100nA @ 3V or 0.3μW [22]. Lastly, the Bluetooth module will only consume power for short periods of time when the user connects to the phone app. When the radio is disabled it operates at 3μA @ 3V or 9μW [23]. When the module is connected it consumes 660μA @ 3V or 1.98mW. Since the radio is disabled for majority of the operating time (~90%) the average consumption would be 0.21mW, which is found by added the weighted sums of the two operation modes. Finally, adding all the components totals a power dissipation of 240mW. The battery has a capacity of 4.5Wh. Using Equation 2 shows that Don't Sweat It can provide up to 18.75 hours of usage on a single charge.

$$E = P \times t \text{ or } t = E/P \tag{Eqn. 2}$$

5 FDA Approval

The path to development and FDA approval will be through the Class II direct De Novo process. We would not apply for the Early Feasibility Studies because non-clinical testing of the watch is readily available and noninvasive. The risk of the watch would also be equal to the risk of individuals using other wearable electronic devices that are already on the consumer market that may not have FDA approval. We would conduct a traditional feasibility study to capture preliminary safety and effectiveness then perform a pivotal study using a number of test subjects. Next would be the pivotal study to definitively study the safety and effectiveness. Then, we would submit a pre-submission to the FDA . The pre-submission provides feedback from the premarket review division that would greatly help in approval of our novel device. Finally, we would create a De Novo request for a Class II device since there are no 510(k) substantially equivalent devices to our design. The watch would be Class II because there is a moderate or controlled risk of a wearable electronic device. The proposal would include the data collected in the feasibility studies. Once the De Novo request is granted, we would legally market the watch.

The timeline for approval would be as follows. After sending in the De Novo request, the FDA would conduct an acceptance review. Within 15 days of the Document Control Center receiving the request, the FDA would notify us of the acceptance review result. If it is accepted for substantiative review, the final step is the De Novo request decision which would be made in 150 review days. This means that we could expect a decision 150 days after the initial document submission.

6 Conclusion

This proposal was for the new medical sensing device Don't Sweat It. It is the next logical evolution of wearable sensing devices for health monitoring. The use of sweat analytes to indicate different health factors along with stress is viable and non-invasive. Don't Sweat It will be beneficial to everyday consumers to monitor and maintain stress levels. It will also be useful in clinical settings for diagnoses of cortisol related diseases. The path to FDA approval will be through the Class II direct De Novo process. Don't Sweat it will help individuals monitor their health real-time and aide in lifestyle changes necessary to curb chronic stress.

References

[1] American Psychological Association, "Stress in America™ 2020: Stress in the Time of COVID-19, Volume One," American Psychological Association. [Online]. Available: https://www.apa.org/news/press/releases/stress/2020/report. [Accessed: 10-Nov-2020].

[2] R. K. Nirmita Panchal, "The Implications of COVID-19 for Mental Health and Substance Use," KFF, 21-Aug-2020. [Online]. Available: https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/. [Accessed: 10-Nov-2020].

[3] Mayo Clinic Staff, "Chronic stress puts your health at risk," Mayo Clinic, 19-Mar-2019. [Online]. Available: https://www.mayoclinic.org/healthy-lifestyle/stress-management/in-depth/stress/art-20046037. [Accessed: 18-Nov-2020].

[4] You and Your Hormones, 2019. [Online]. Available: https://www.yourhormones.info/hormones/cortisol/. [Accessed: 18-Nov-2020].

[5] T. Kubota, "A wearable device measures cortisol in sweat," Stanford News, 20-Jul-2018. [Online]. Available: https://news.stanford.edu/2018/07/20/wearable-device-measures-cortisol-sweat/. [Accessed: 30-Nov-2020].

[6] M. Shnur, "Elevated Lactate – Not just a marker for sepsis and septic shock," Nursing Blog | Lippincott NursingCenter. [Online]. Available: https://www.nursingcenter.com/ncblog/march-2017/elevated-lactate-%E2%80%93-not-just-a-marker-for-sepsis-an. [Accessed: 30-Nov-2020].

[7] T. Alsop, "Topic: Fitbit," Statista. [Online]. Available: https://www.statista.com/topics/2595/fitbit/. [Accessed: 30-Nov-2020].

[8] "National Diabetes Statistics Report, 2020," Centers for Disease Control and Prevention, 11-Feb-2020. [Online]. Available: https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html. [Accessed: 30-Nov-2020].

[9] D. Curry, "Calm Revenue and Usage Statistics (2020)," Business of Apps, 30-Oct-2020. [Online]. Available: https://www.businessofapps.com/data/calm-statistics/. [Accessed: 30-Nov-2020].

[10] Abbott Laboratories, Continuous Glucose Monitoring System. [Online]. Available: https://www.freestylelibre.us/. [Accessed: 18-Nov-2020].

[11] W. D. McArdle, F. I. Katch, and V. L. Katch, Essentials of exercise physiology. Philadelphia, Baltimore: Wolters Kluwer, 2016.

[12] R. P. Taylor, A. Polliack, and D. Bader, "The analysis of metabolites in human sweat : analytical methods and potential application to investigation of pressure ischaemia of soft tissues," Sage Journals, vol. 31, no. 1, 1994.

[13] Y. J. Hong, H. Lee, J. Kim, M. Lee, H. J. Choi, T. Hyeon, and D.-H. Kim, "Blood Sugar Monitoring: Multifunctional Wearable System that Integrates Sweat-Based Sensing and Vital-Sign Monitoring to Estimate Pre-/Post-Exercise Glucose Levels (Adv. Funct. Mater. 47/2018)," Advanced Functional Materials, vol. 28, no. 47, p. 1870336, 2018.

[14] M. Yokus, T. Songkakul, V. Pozdin, A. Bozkurt, and M. Daniele, "Wearable multiplexed biosensor system toward continuous monitoring of metabolites," *Biosensors and Bioelectronics*, vol. 153, 2020.

[15] Mayo Clinic Staff, "Diabetic coma," Mayo Clinic, 26-Jun-2020. [Online]. Available: https://www.mayoclinic.org/diseases-conditions/diabetic-coma/symptoms-causes/syc-20371475. [Accessed: 18-Nov-2020].

[16] M. Chung, G. Fortunato, and N. Radacsi, "Wearable flexible sweat sensors for healthcare monitoring: A review: Request PDF," ResearchGate, 2019. [Online]. Available: https://www.researchgate.net/publication/336372972_Wearable_flexible_sweat_sensors_for_healthcare_monitoring_A_review. [Accessed: 30-Nov-2020].

[17] M. Hardie, "Left Out in the Lab: What Reagents Survive Ambient Temperatures?," GoldBio. [Online]. Available: https://www.goldbio.com/articles/article/left-out-in-the-lab- what-reagents-survive-ambient-temperatures. [Accessed: 30-Nov-2020].

[18] A. Weltin, J. Kieninger, and B. Enderle, "Polymer-based, flexible glutamate and lactate microsensors for in vivo applications," Biosensors & bioelectronics. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/24880657/. [Accessed: 30-Nov-2020].

[19] Silicon Labs, "EFM32 Gecko Family EFM32TG Data Sheet," EFM32 datasheet, Mar. 2010 [Revised Jul. 2020]

[20] Eastrising Technology Co., Limited, "TFT LCD Display Module Datasheet," ER-FTM1.44- 2 datasheet, Dec. 2019

[21] Texas Instruments, "OPA857 Ultralow-Noise, Wideband, Selectable-Feedback Resistance Transimpedance Amplifier," OPA857 datasheet, Dec. 2013 [Revised Aug. 2016]

[22] Texas Instruments, "SN74HCS14 Hex Inverter with Schmitt-Trigger Inputs," SN74HCS14 datasheet, Jan. 2020 [Revised Jun. 2020]

[23] Silicon Labs, "BGX13S Blue Gecko Xpress Bluetooth ® SiP Module Data Sheet," BGX13S datasheet, Aug. 2018 [Revised Nov. 2019]